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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,223	12/15/2004	Ning Man Cheng	B001.001.NPRUS	7018

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,223	CHENG ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26-29,32 and 35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24,26-29,32 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

Claims 24, 26-29, 32 and 35-37 are currently pending in the instant application.

In response to a previous Office action, a non-final requirement (mailed on October 23, 2006), Applicants filed a response and amendment received on January 19, 2007, amending claims 24, 26-29, 32, and adding new claims 35-37 is acknowledged. Claims 1-23 remain withdrawn and claims 25, 30-31 and 33-34 are cancelled.

Claims 24, 26-29, 32, and 35-37 are under consideration and will be examined herein.

Applicants' arguments filed on January 19, 2007 have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

New-Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). The last claim number should be 37 not 38, because the previous claim of the last claim is 36. Appropriate correction is required.

Withdrawn Claim Rejections - 35 U.S.C. § 112(2)

Previous rejection of claims 25 and 26 under 35 USC § 112, second paragraph, as being indefinite is withdrawn in view of applicants cancellation of claims 25, 30-31 and 34.

Previous rejection of claim 29 under 35 USC § 112, second paragraph, as being indefinite in the recitation "substantially free of protein degradation inhibitor" is withdrawn in view of deleting said phrase.

Previous rejection of claim 30 under 35 USC § 112, second paragraph, as being indefinite is withdrawn in view of applicants cancellation of claim 30.

Previous rejection of claim 33 under 35 USC § 112, second paragraph, as being indefinite is withdrawn in view of applicants cancellation of claim 33.

New-Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 32 is indefinite and vague in the recitation of "said composition modified recombinant arginase I said modification" which is confusing and does not make any sense. Is the statement intended to be "said composition comprising modified recombinant arginase I having a modification ---"? Clarification is required.

Claims 29 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Claim 29 is indefinite and vague in the recitation of "method is performed in absence of protein degradation inhibitor", which is vague and confusing. The specification discusses only using a composition lacking a protease inhibitor. Protease inhibitors are usually used in vitro for inhibiting protein degradation, which are toxic and non-ingestible. Therefore, a composition for treating human should be devoid of protease inhibitor. Clarification is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112 (1)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Previous rejection of claims 25-32 and 34 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of applicants cancellation of claims 25, 30-31 and 34.

Previous rejection of claims 25-32 and 34 under 35 U.S.C. 112, first paragraph, as failing to comply with Scope and Enablement requirement is withdrawn in view of applicants cancellation of claims 25, 30-31 and 34.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 26-29, 32 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 24, 26-29, 32 and 35-37 are directed to a method of treatment of human malignancies, comprising administering to a patient of any modified arginase I or any composition comprising any modified arginase I or any composition that reduces the physiological arginine level.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical*).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both *Lily* and *Enzo Biochemical* to methods of using products, wherein said products lack adequate written description. While in *University of Rochester v.*

G.D. Searle & Co. the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description (see *Enzo* paraphrase above).

Thus, Claims 24, 26-29, 32 and 35-37 are directed to a method of treatment of human malignancies, comprising administering to a patient of any modified arginase I or any composition comprising any modified arginase I or any composition that reduces the physiological arginine level.

Claims are thus drawn to a process of using any modified arginase I for treating malignancies having arginine degrading activity, wherein said modified proteins structures are not fully described in the specification. No information, beyond the characterization of a modified arginase protein, which would indicate that applicants had possession of the claimed genus of any modified arginase I or any composition comprising any modified arginase I having arginine degrading activity. The specification does not contain any disclosure of the structure of all the mutants or variants of any arginase I or any composition comprising any modified arginase I used in the method of the claim. The genus of polypeptides used in the method is a large variable genus including mutants and variants, which can have wide variety of structures. Therefore, many structurally unrelated polypeptides are encompassed within the scope of the method claims. The specification discloses the structure of only a single representative species of the claimed genus i.e. human arginase I modified by pegylation, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed

genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 24, 26-29, 32 and 35-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment of human malignancy, comprising administering of a modified human arginase I of SEQ ID NO: 9 modified by pegylation (i.e. treatment of said protein with polyethylene glycol) or a composition comprising said human arginase I of SEQ ID NO: 9 modified by pegylation, does not reasonably provide enablement for a method of treatment of any malignancies, comprising administering of any modified human arginase I or any composition comprising any modified human arginase I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 24, 26-29, 32 and 35-37 are so broad as to encompass a method of treatment of any malignancies using any modified human arginase or any composition comprising any modified human arginase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of modified human arginase including mutants or variants broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity

requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one human arginase and modification by treating with polyethylene glycol.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims which encompass a method of treatment of any malignancies using any modified human arginase I or any composition comprising any modified human arginase I because the specification does **not** establish: (A) regions of the protein structure which may be modified without affecting arginase activity; (B) the general tolerance of arginase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any arginase amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of treatment of any malignancies using any modified human arginase I or any composition comprising any modified human arginase I. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any modified arginase I having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Withdraw- Claim Rejections - 35 USC § 102

Previous rejection of Claims 24-27 under 35 U.S.C. 102(b) as being anticipated by Vockley et al. (US 6316,199 B1, issue date 11/13/2001) is withdrawn in view of applicant's amendment to claims and persuasive arguments.

Applicants argue that claim 24 has been amended to recite modified recombinant human arginase I, and further argue that Vockley discloses only recombinant human arginase II and its use and Vockley fails to teach modified recombinant human arginase I.

Vockley et al. teach type II human arginase and use of said arginase II for reducing arginine in a symptom of hyperargininemia and for treating cancer due to defects of arginase II gene. Vockley et al. do not teach or suggest that arginase I could be used for treating cancer. Therefore, Vockley et al. do not anticipate instant claims as amended and the rejection is withdrawn.

New-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 24, 26-29, 32 and 35-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Tepic et al. (WO/2003/063780, publication 7/8/2003, claim priority of provisional application 60/350,971 filed on 1/25/2002, see IDS). Instant claims are drawn to a method of treatment of human malignancies, comprising administering modified recombinant-human arginase I, said modification resulting in an extended half-life, wherein said human malignancies are selected from the group consisting of: liver tumor, breast cancer, and rectal cancer and the human arginase I is modified by pegylation i.e. treating with polyethylene glycol.

Tepic et al. teach a therapeutic composition and a method for the treatment of cancer by depletion of arginine without systemic complications comprising an arginine decomposing enzyme i.e. type I liver human arginase, wherein the enzyme is partially purified and recombinant (abstract and p7, paragraph 1 and 2). Tepic et al. also teach that the enzyme is modified by pegylation to increase circulation half-life. Tepic et al. also teach that said composition may be administered as a drug for treating cancer including liver cancer. Therefore, Tepic et al. anticipate claims 24, 26-29, 32 and 35-37 of the instant application.

Conclusion

Claims 24, 26-29, 32, and 35-37 are pending.

Claims 24, 26-29, 32, and 35-37 are rejected.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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